# Pesticide Toxicity

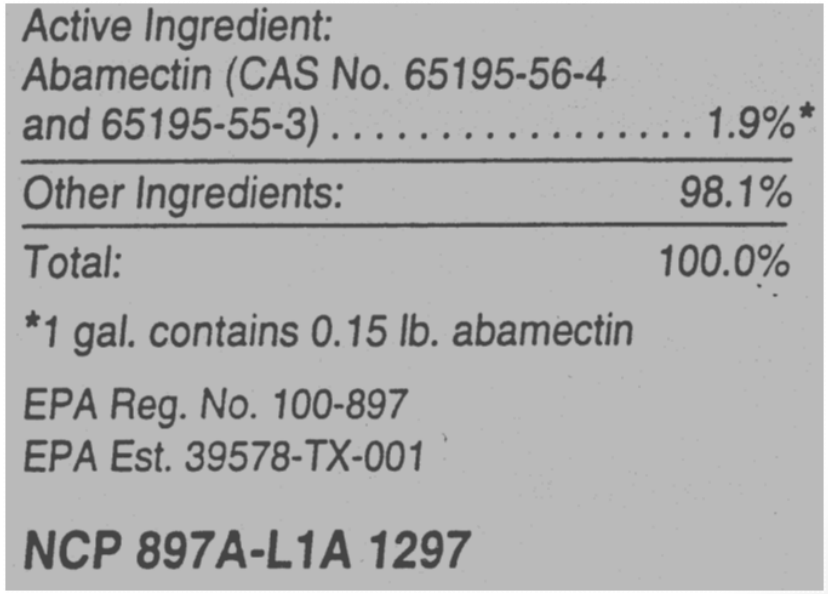
# Definition of Pesticide

- ✓ Pest = unwanted creature or living,
- ✓ Cide = killing or elimination.
- ✓ Any substance or mixture of substances deliberately added to the environment and intended for **preventing, destroying, repelling, or mitigating pests**

- ✓ Pesticides may be more specifically identified as **insecticides** (insects), **herbicides** (weeds), **fungicides** (fungi and molds), **rodenticides** (rodents), **acaricides** (mites), **molluscides** (snails and other mollusks), **miticides** (mites), **larvicides** (larvae), and **pediculocides** (lice)

# Use of pesticides

- Pesticides are often, if not always, used as **multi-agent formulations**, in which the **active ingredient is present together with other ingredients** to allow mixing, dilution, application, and stability…."**inert" or "other"** (**e.g., formaldehyde, sulfuric acid, benzene, toluene, other organic solvents** )



| | |
|---|---|
| *Active Ingredient:* | |
| *Abamectin (CAS No. 65195-56-4 and 65195-55-3)* | *1.9%** |
| *Other Ingredients:* | *98.1%* |
| *Total:* | *100.0%* |

**1 gal. contains 0.15 lb. abamectin*

*EPA Reg. No. 100-897*
*EPA Est. 39578-TX-001*

***NCP 897A-L1A 1297***

# "Others"

- "Others": Though they do not have pesticidal action, such **inert ingredients** may not always be devoid of toxicity, thus, an ongoing task of manufacturers and regulatory agencies is to assure that inert ingredients do not pose any unreasonable risk of adverse health effects

# US Pesticide Use

- 4.5 billion pounds chemicals per year
  - 890 active ingredients, 30,000 formulations
  - Uses
    - **75% agricultural**
    - **25% home, garden**

# Exposure

- Exposure to pesticides can occur via the **oral** or **dermal** routes or by **inhalation**
- **High oral doses,** leading to severe poisoning and death, are achieved as a result of pesticide ingestion for suicidal intent, or of accidental ingestion, commonly due to storage of pesticides in improper containers
- **Chronic low doses,** on the other hand, are consumed by the general population as pesticide residues in **food** or as contaminants in **drinking water**

# Exposure

- **Workers i**nvolved in the production, transport, mixing and loading, and application of pesticides, as well as in harvesting of pesticide-sprayed crops, are at the highest risk for pesticide exposure
- **Dermal exposure during normal handling or application of pesticides**, or in case of accidental spillings, occurs in body areas not covered by protective clothing, such as the face or the hands, or by inhalation
- Furthermore, pesticides deposited on **clothing may penetrate the skin** and/or potentially expose others, if clothes are not changed and washed on termination of exposure

# Human Poisoning

- Pesticides are **not always selective** for their intended target species…..adverse health effects can occur in non-target species, including humans

- Several million poisonings and a couple hundred thousand of deaths….World Health Organization **(WHO) classified pesticides by hazard**, where acute oral or dermal toxicities in rats were considered

# Table 22–1 WHO-recommended classification of pesticides by hazard (2009).

| WHO Class | | LD50 for the rat (mg/kg body weight) | |
|---|---|---|---|
| | | Oral | Dermal |
| Ia | Extremely hazardous | < 5 | < 50 |
| Ib | Highly hazardous | 5–50 | 50–200 |
| II | Moderately hazardous | 50–2000 | 200–2000 |
| III | Slightly hazardous | Over 2000 | Over 2000 |
| U | Unlikely to present acute hazard | 5000 or higher | |

# Diagnosis of Pesticide Toxicity

- **Exposure history (most important)**
  - Occupational and environmental history
  - Duration, dose, route of potential exposure
  - information about the patient's job, home use of chemicals, and proximity of residence to industrial sites, including agriculture
- **Symptom review**
  - Important to remember that symptoms may be caused by "**inert" ingredients** and therefore may not be typical of the active pesticidal ingredient in a **formulation**
- **Physical exam and lab findings**

**Table 1** The main groups of pesticides.

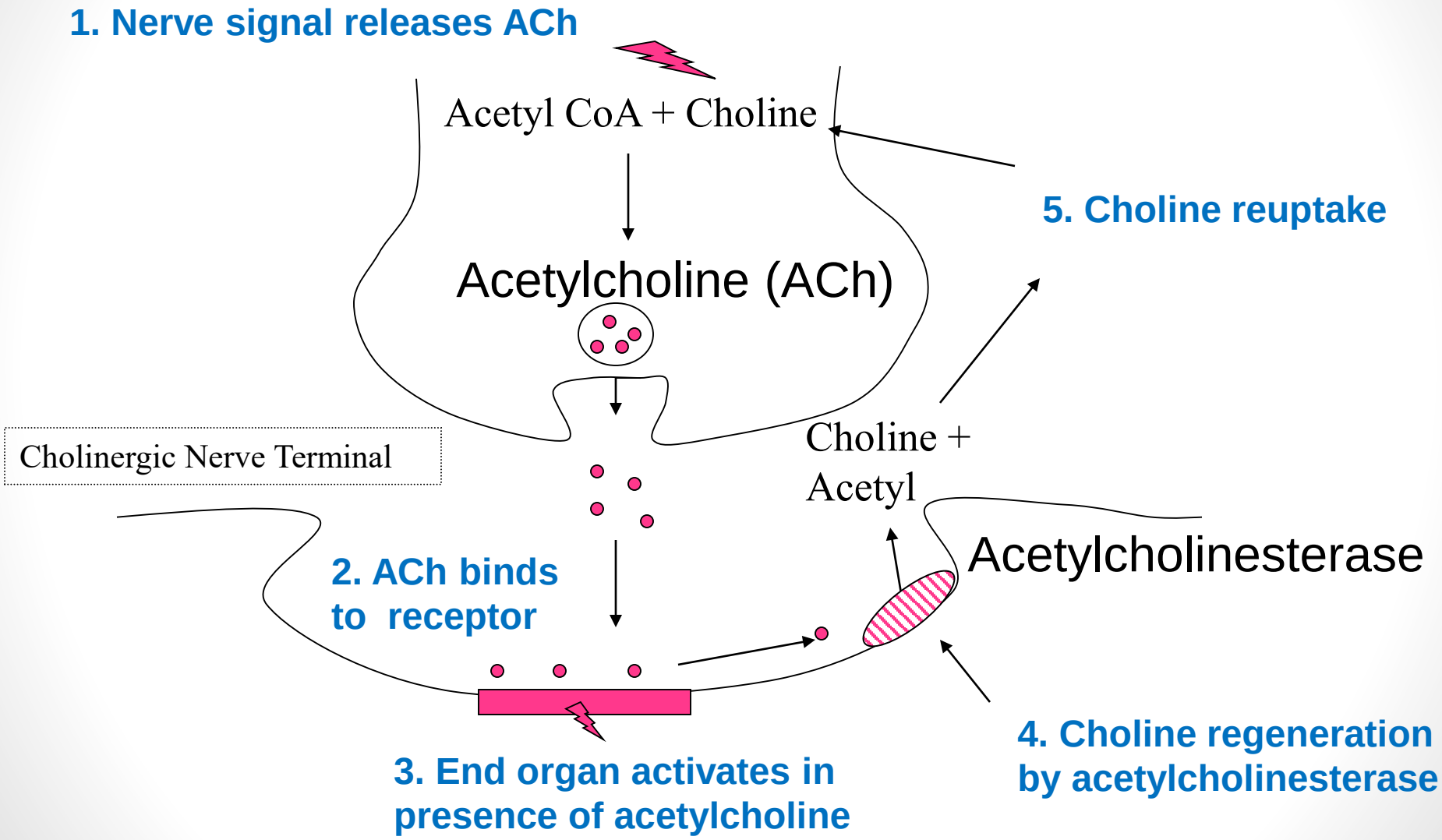
| Group | Subgroups | Examples |
|---|---|---|
| Organochlorines (OCs) | | DDT<br>Endrin<br>Aldrin<br>Dieldrin<br>Endosulfan<br>$\gamma$-Hexachlorocyclohexane (lindane) |
| Anticholinesterases | Organophosphates (OPs) | Malathion<br>Fenitrothion<br>Dichlorvos<br>Diazinon |
| | Carbamates | Carbaryl<br>Aldicarb |
| Pyrethrins and synthetic pyrethroids | | Pyrethrum<br>Permethrin<br>Cypermethrin<br>Flumethrin |
| Natural compounds, other than pyrethrins | | Abamectin<br>Ivermectin<br>Rotenone<br>Nicotine |
| Substances which interfere with systems specific to insects | Juvenile hormone analogues<br>Chitin synthesis inhibitors<br>Ecdysone agonists | Cyromazine<br>Diflubenzuron<br>Tebufenozide |
| Miscellaneous synthetic insecticides | Formamidine<br>$GABA_A$ blocker | Amitraz<br>Fipronil |

Ballantyne et al (ed.) *General and Applied Toxicology*, 1999

# Insecticides

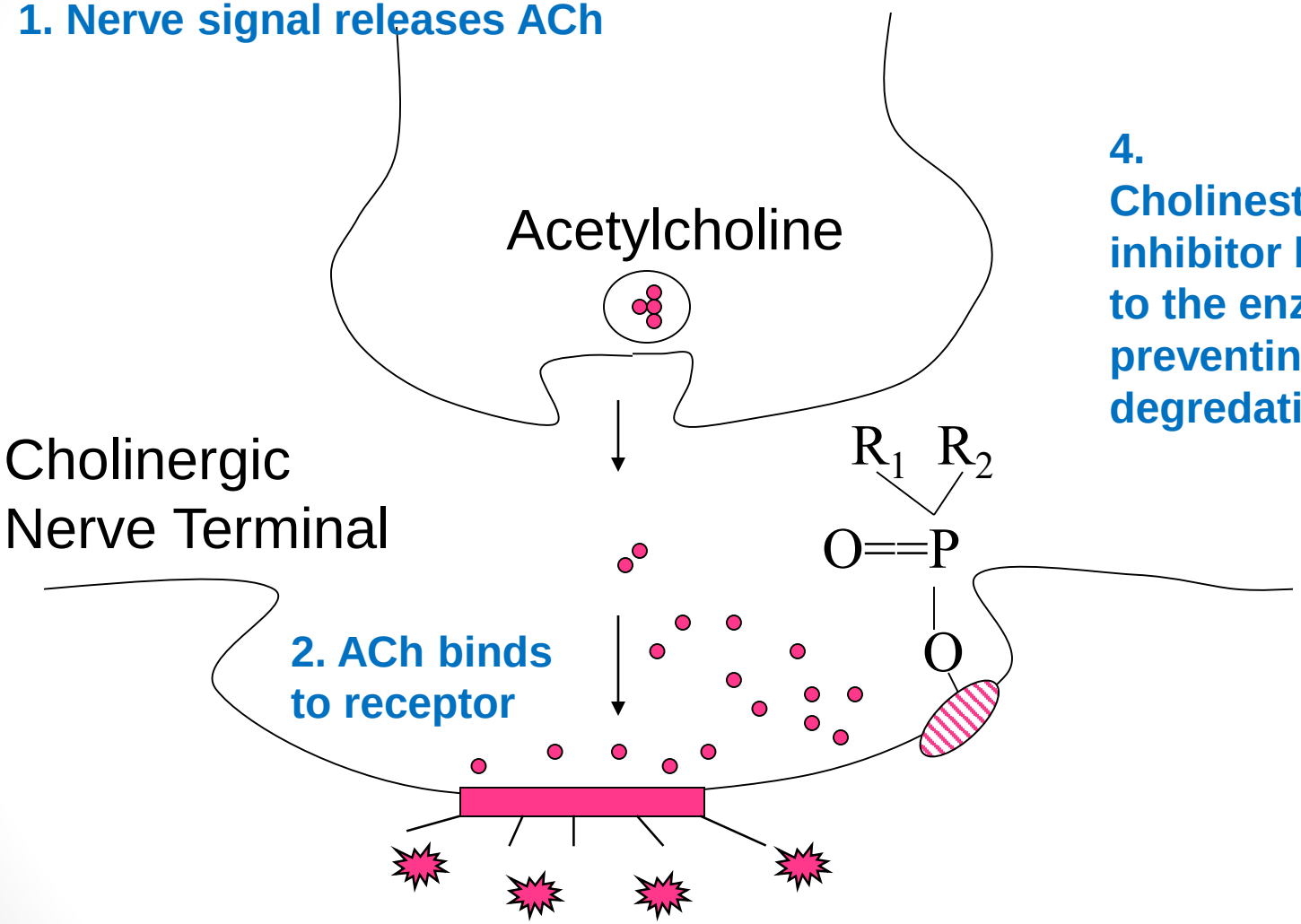
- All of the chemical insecticides in use today are **neurotoxicants**, and act by poisoning the nervous systems of the target organisms
- **Cholinesterase Inhibitors**
  - Carbamates
  - Organophosphates
- **Pyrethrins & Pyrethroids**
- **Organochlorines**

# Cholinesterase Normal Function



# Inhibition of Cholinesterase

**1. Nerve signal releases ACh**




**4. Cholinesterase inhibitor binds to the enzyme, preventing Ach degredation**

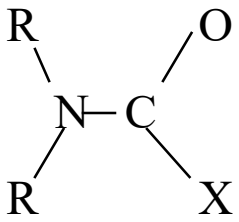
**3. Activity of end organ does not cease**

# Cholinesterase Blood Tests

- Two cholinesterase enzymes
  - RBC, NMJ and neural synapses
    - “true”/ acetylcholinesterase
  - Plasma
    - “pseudo”/ butyrylcholinesterase

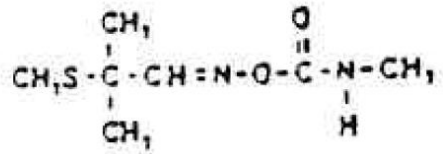
# Insecticides: Cholinesterase Inhibitors

- **N-methyl Carbamates** (carbamic acid)
  - **Carbaryl, Carbofuran, Aldicarb**




Generic structure for N—methyl carbamates

- Dermal **skin penetration** by carbamates is **increased by organic solvents and emulsifiers** present in most formulations
- Carbamates inhibit AChE **reversibly**……susceptible to a variety of enzyme-catalyzed biotransformation reactions, (oxidation and hydrolysis)

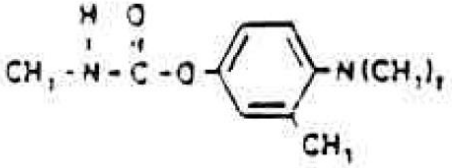


Aldicarb
(Temik)

Propanal, 2-methyl-2-(methylthio)-,
O-[(methylamino) carbonyl] oxime

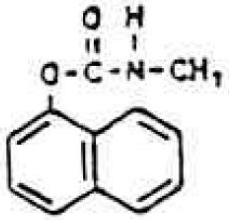
Bendiocarb
(Ficam)

1,3-Benzodioxol-4-ol, 2,2-dimethyl-,
methylcarbamate



Aminocarb
(Matacil)

Phenol, 4-(dimethylamino)-3-methyl-,
methylcarbamate



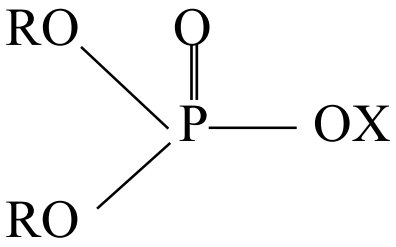
Carbaryl
(Sevin)

1-Naphthalenol, methylcarbamate

Names and chemical structures of some carbamate insecticides.

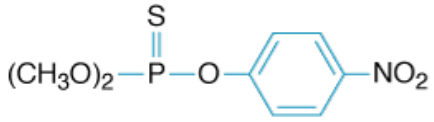
# Insecticides: Cholinesterase Inhibitors

- **Organophosphates (OPs)**
  - **Chlorpyrifos, Diazinon, Malathion**

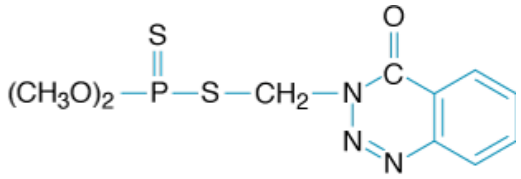



Generic structure for organophosphates

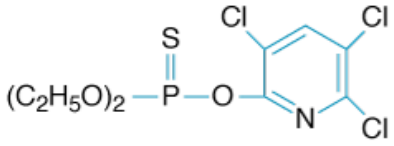
  - Compounds that contain a **sulfur** bound to the **phosphorus**, **metabolic bioactivation is necessary** for their biological activity to be manifest…..only compounds with a **P=O** moiety are effective inhibitors of AChE



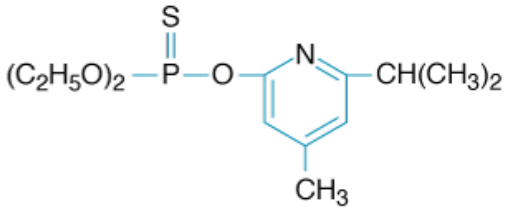
Methylparathion



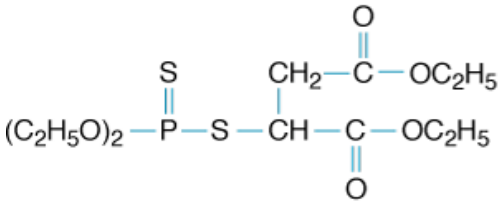
Azinphosmethyl (Guthion)



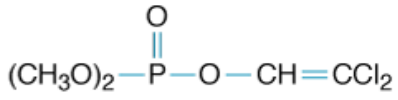
Chlorpyrifos



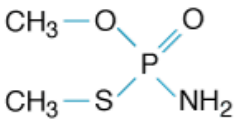
Diazinon



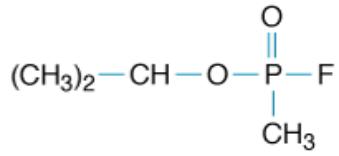
Malathion



Dichlorvos



Metamidophos



Sarin



- Structures of some organophosphorus insecticides and of the nerve agent sarin
- Most commonly used compounds are organophosphorothioates (i.e., have a P=S bond), but **some, including sarin, have a P=O bond and do not require metabolic activation**

# Insecticides: organophosphate

- Phosphorylated AChE is hydrolyzed slowly, and the rate of "**spontaneous reactivation**" depends **on the chemical nature of the R substituents**

- When there is a loss of one of the two alkyl (R) groups, the enzyme-inhibitor complex has "**aged**“ and reactivation of phosphorylated AChE does not occur

- The enzyme is considered to be **irreversibly inhibited, and synthesis of the new enzyme** is required to restore activity, a process that may take days

Table 22–4 Signs and symptoms of acute poisoning with anticholinesterase compounds.

| Site and Receptor Affected | Manifestations |
|---|---|
| Exocrine glands (M) | Increased salivation, lacrimation, perspiration |
| Eyes (M) | Miosis |
| Gastrointestinal tract (M) | Abdominal cramps, vomiting, diarrhea |
| Respiratory tract (M) | Increased bronchial secretion, bronchoconstriction |
| Bladder (M) | Urinary frequency, incontinence |
| Cardiovascular system (M) | Bradycardia, hypotension |
| Skeletal muscles (N) | Muscle fasciculations, twitching, cramps, generalized weakness, flaccid paralysis |
| Central nervous system (M, N) | Dizziness, lethargy, fatigue, headache, mental confusion, depression of respiratory centers, convulsions, coma |

M: muscurinic receptor
N: nicotininc receptor

# Commonly-used Acronyms for Cholinesterase Inhibition Syndromes

- Salivation
- Lacrimation
- Urination
- Diarrhea

- Defecation
- Urination
- Miosis
- Bronchospasm
- Excessive salivation
- Lacrimation
- Salivation sweating

# Treatment of Pesticide Intoxication

## Decontamination

- Procedures aimed at decontamination and/or at minimizing absorption **depend on the route of exposure.**

  - **Dermal exposure**: contaminated clothing should be removed, and the **skin washed with soap.** Scrub under fingernails

  - **Ingestion**: administer **activated charcoal or gastric lavage in case of large ingestions, caution**: possibility of seizures or rapidly changing mental status

# Specific Management for AChI Poisoning

- **Respiratory distress**: maintain **ABC;** Oxygen, bronchodilators if indicated
- **Atropine** (i.v), (**muscarinic receptor** antagonist), prevents the action of accumulating acetylcholine on these receptors
- Administration of **pralidoxime** (2-PAM) early after exposure can **help prevent AChE aging**
- **Diazepam** may be used to relieve **anxiety in mild cases, and control convulsions in the more severe cases**

# Treatment: Atropine

- Reverses DUMBELS syndrome
- Give **atropine in escalating doses** until **clinical improvement is evident**. Begin with 2–5 mg IV initially
- Double the dose administered every 5 minutes until respiratory secretions have cleared.
- ***Note:*** Atropine will reverse **muscarinic** but not nicotinic effects

# 2-PAM Treatment Regimen

- **Loading dose** (30–50 mg/kg, total of 1–2 g in adults) over 30 minutes
- followed by **a continuous infusion** of 8–20 mg/kg/h
- Most effective if **started early,** before aging
- but may still be effective if given **later,** particularly after exposure to **highly lipid-soluble compounds** released into the blood from fat stores over days to weeks
- Continue **pralidoxime for 24 hours after the patient becomes asymptomatic, or at least as long as atropine infusion is required**

# Insecticides

- All of the chemical insecticides in use today are **neurotoxicants**, and act by poisoning the nervous systems of the target organisms
- **Cholinesterase Inhibitors**
  - Carbamates
  - Organophosphates
- **Pyrethrins & Pyrethroids**
- **Organochlorines**

# Insecticides
# Pyrethrins & Pyrethroids

- Pyrethrins
  - **Natural** insecticides developed from extracts of the flower head of *Chrysanthemum cinerariaefolium*
- Pyrethroids
  - **Synthetic** derivatives
  - Used with piperonyl butoxide to

  Prolong their activity

# Pyrethroid Insecticides

- Pyrethroids now account **for >25% of the global insecticide market.**

  - ✓ High insecticidal potency
  - ✓ Relatively low mammalian toxicity (not well absorbed from skin and GIT),
  - ✓ low tendency to induce insect resistance.

- **used widely as insecticides in :**

  - ✓ in the house and in **agriculture**,
  - ✓ in medicine topically for Tx of **scabies and head lice**
  - ✓ in tropical countries as soaks to prevent **mosquito bites**

# Pyrethrins & Pyrethroids

## Mechanism of Toxicity

- They are **axonic poisons** and cause paralysis of an organism
- The chemical causes paralysis by **keeping the sodium channels open** in the neuronal membranes of an organism
- Pyrethroids are rapidly **metabolized** through both phase I and phase II reactions (**hydrolysis and oxidation as well as conjugation)**

# Pyrethroids Toxicity

- **Dermal contact** with pyrethroids is **paresthesia** (from a direct effect on cutaneous nerve endings)
- Symptoms include **continuous tingling & tickling** or, when more severe, **burning**
- **Ingestion** of large doses resulting in **seizures, coma, or respiratory arrest**.
- Chronic studies indicate that at high dose levels, they cause **slight liver enlargement** accompanied by some histopathologic changes
- Little evidence of teratogenicity and mutagenicity

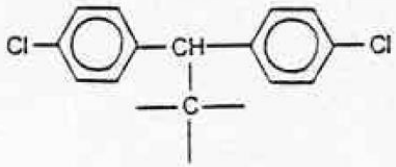
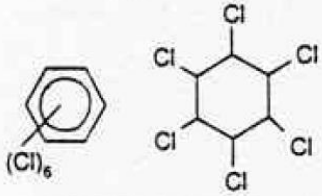
# Pyrethroid Toxicity Treatment


- Symptomatic relief
- Decontamination
- Topical application of vitamin E?? (in part due to sequestration of lipophilic pyrethroid into the vitamin E)
- administer activated charcoal orally
- **Enhanced elimination.** …no role…rapidly metabolized

# Insecticides: Organochlorines

- Chlorinated ethane derivatives (DDT) (prototype)
- Cyclodienes (Chlordane, aldrin, dieldrin, heptachlor, endrin, toxaphene)
- Hexachlorocyclohexane (Lindane)

**Table 22–5**
**Structural Classification of Organochlorine Insecticides**

| | | |
|---|---|---|
| Dichlorodiphenylethanes |  | DDT, DDD<br>Dicofol<br>Perthane<br>Methoxychlor<br>Methlochlor |
| Cyclodienes |  | Aldrin, Dieldrin<br>Heptachlor<br>Chlordane<br>Endosulfan |
| Chlorinated Benzenes<br>Cyclohexanes |  | HCB, HCH<br>Lindane (*a*-BHC) |

# DDT and Its Analogs

- **DDT** effective against agricultural pests, and insects that transmit serious diseases (malaria & yellow fever)
- DDT has a **moderate oral acute toxicity** and its **dermal absorption is very limited**
- The earliest symptom DDT poisoning is **pyresthesia** of the mouth and lower part of the face
- **High doses** also causes **motor unrest, increased frequency of spontaneous movements, followed by the development of tremors, and eventually convulsions**

# DDT and Its Analogs

- Both in insects and in mammals, DDT **interferes with the sodium channels in the axonal membrane** by a mechanism similar to that of pyrethroids
- An important target for chronic DDT exposure is the liver……**cause hepatic cell hypertrophy and necrosis**
- **Potent inducers of cytochrome P450s**
- Both **DDE** and **DDD** (**breakdown product),** are **carcinogenic** in rodents, causing primarily an increase in **hepatic tumors**

# Hexachlorocyclohexanes and Cyclodienes

- These two families of **organochlorine insecticides** comprise a large number of compounds that share a similar mechanism of neurotoxic action
- **Lindane** and **cyclodienes** have moderate to high acute oral toxicity….readily absorbed through the skin
- The primary target for their toxicity is the **CNS**….. **binds to the chloride channel, blocking its opening** and **antagonizing GABA action**
- Tremor is absent, but **convulsions** are a prominent aspect of poisoning

# Other Insecticides

**Rotenoids** At least six rotenoid esters (rotenone)

- Isolated from *Derris* root
- Toxicity due to its ability to inhibit, at nanomolar conc the **mitochondrial respiratory chain**
- Toxicity varies greatly in different species.
- Low acute toxicity in humans, but causes allergic reactions.
- **Poisoning symptoms**: increased respiratory and cardiac rates, muscular depression, followed by respiratory depression

# The main targets and classes of insecticides